

09/889,330

Atty. Docket No. 249/146US

AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph beginning at line 24 of page 2 with the following amended paragraph:

The exendins have some sequence similarity to several members of the glucagon-like peptide family, with the highest homology, 53%, being to glucagon-like peptide-1 (GLP-1) [7-36] NH₂ [SEQ. ID. NO. 3] (Goke, et al., J. Biol. Chem., 268: 19650-55, 1993). GLP-1 [7-36] NH₂ is also known as proglucagon [78-107], or simply "GLP-1" as used most often herein. GLP-1 has an insulinotropic effect, stimulating insulin secretion from pancreatic beta cells. GLP-1 has also been reported to inhibit glucagon secretion from pancreatic alpha-cells (Orsov, et al., Diabetes, 42: 658-61, 1993; D'Alessio, et al., J. Clin. Invest., 97: 133-38, 1996). The amino acid sequence of GLP-1 is shown in Figure 3. GLP-1 has been reported to inhibit gastric emptying (Willms B, et al., J Clin Endocrinol Metab 81 (1): 327-32, 1996; Wettergren A, et al., Dig Dis Sci 38 (4): 665-73, 1993), and gastric acid secretion (Schjoldager BT, et al., Dig Dis Sci 34 (5): 703-8, 1989; O'Halloran DJ, et al., J Endocrinol 126 (1): 169-73, 1990; Wettergren A, et al., Dig Dis Sci 38 (4): 665-73, 1993)). GLP-1 [7-37], which has an additional glycine residue at its carboxy terminus, also stimulates insulin secretion in humans (Orsov, et al., Diabetes, 42: 658-61, 1993). A transmembrane G-protein adenylate-cyclase-coupled receptor said to be responsible at least in part for the insulinotropic effect of GLP-1 has reportedly been cloned from a beta-cell line (Thorens, Proc. Natl. Acad. Sci. USA 89: 8641-45, 1992).

Please replace the paragraph beginning at line 3 of page 6 with the following amended paragraph:

Exendin-4 [9-39] is also reported to act as an antagonist of the full length exendins, inhibiting stimulation of pancreatic acinar cells by exendin-3 and exendin-4 (Raufman, et al., J. Biol. Chem. 266: 2897-902, 1991; Raufman, et al., J. Biol. Chem., 266: 21432-37, 1992). It is also reported that exendin [9-39] inhibits the stimulation of plasma insulin levels by exendin-4, and inhibits the somatostatin release-stimulating and gastrin release-inhibiting activities of exendin-4 and GLP-1 (Kolligs, F., et al., Diabetes,

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44: 16-19, 1995; Eissele, et al., Life Sciences, 55: 629-34, 1994). Exendin [9-39] has been used to investigate the physiological relevance of central GLP-1 in control of food intake (Turton, M. D. et al. Nature 379: 69-72, 1996). GLP-1 administered by intracerebroventricular (ICV) injection inhibits food intake in rats. This satiety-inducing effect of GLP-1 delivered ICV is reported to be inhibited by ICV injection of exendin [9-39] (Turton, supra). However, it has been reported that GLP-1 does not inhibit food intake in mice when administered by peripheral injection (Turton, M. D., Nature 379: 69-72, 1996; Bhavsar, S. P., Soc. Neurosci. Abstr. 21: 460 (188.8), 1995).

Please replace the paragraph beginning at line 25 of page 51 with the following amended paragraph:

In a preferred injection procedure, the exendin or exendin agonist is administered parenterally, more preferably by injection, for example, by peripheral injection. Preferably, about 1 [[μg]]-30 μg to about 1 mg of the exendin or exendin agonist is administered per day. More preferably, about 1-30 μg to about 500 μg, or about 1-30 μg to about 50 μg of the exendin or exendin agonist is administered per day. Most preferably, depending upon the weight of the subject and the potency of the compound administered, about 3 μg to about 50 μg of the exendin or exendin agonist is administered per day. Preferred doses based upon patient weight for compounds having approximately the potency of exendin-4 range from about 0.005 μg /kg per dose to about 0.2 μg /kg per dose. More preferably, doses based upon patient weight for compounds having approximately the potency of exendin-4 range from about 0.02 μg /kg per dose to about 0.1 μg /kg per dose. Most preferably, doses based upon patient weight for compounds having approximately the potency of exendin-4 range from about 0.05 μg /kg per dose to about 0.1 μg /kg per dose. These doses are administered from 1 to 4 times per day, preferably from 1 to 2 times per day. Doses of exendins or exendin agonists will normally be lower if given by continuous infusion. Doses of exendins or exendin agonists will normally be higher if given by non-injection methods, such as oral, buccal, sublingual, nasal, pulmonary or skin patch delivery.

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Please replace the paragraph beginning at line 23 of page 57 with the following amended paragraph:

Administration via the Gut- Male db/db mice (approximately 50g body [[wt.]] weight) were fasted for 2h and before and after an intra- gastric administration of saline or exendin-4 (exendin-4). A 9% decrease in plasma glucose concentration was observed with 1mg/200µl/animal and a 15% decrease was observed with 3 mg/200µl/animal, compared with a 10% increase plasma glucose in the controls one hour after treatment (see Figure 11).

Please replace the paragraph beginning at line 22 of page 60 with the following amended paragraph:

The solution containing peptide was applied to a preparative C-18 column and purified (10% to 40% Solvent B in Solvent A over 40 minutes). Purity of fractions was determined isocratically using a C-18 analytical column. Pure fractions were pooled furnishing the above-identified peptide. Analytical RP-HPLC (reverse phase - high performance liquid chromatography) (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 19.2 minutes.